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APPLICATION NO. FILING DATE FIRST NAMED INVENTOR ATTORNEY DOCKET NO. CONFIRMATION NO. 10/053,530 01/17/2002 Jeffrey A. Ledbetter 30906/41458UTL2 8993 4743 EXAMINER 01/17/2006 7590 MARSHALL, GERSTEIN & BORUN LLP BLANCHARD, DAVID J 233 S. WACKER DRIVE, SUITE 6300 PAPER NUMBER **SEARS TOWER** ART UNIT CHICAGO, IL 60606 1643

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

			on No.	Applicant(s)		
Office Action Summary		10/053,53	ю.	LEDBETTER ET AL.		
		Examiner		Art Unit		
		David J. B	lanchard	1643		
The MAILING DATE of this communication appears on the cover sheet with the correspondence address Period for Reply						
WHICH - Extensi after Si - If NO po - Failure Any rep	RTENED STATUTORY PERIOD FOR I IEVER IS LONGER, FROM THE MAILI ons of time may be available under the provisions of 37 X (6) MONTHS from the mailing date of this communica- eriod for reply is specified above, the maximum statutory to reply within the set or extended period for reply will, be ly received by the Office later than three months after the patent term adjustment. See 37 CFR 1.704(b).	NG DATE OF TH CFR 1.136(a). In no evention. y period will apply and wing y statute, cause the apply	IIS COMMUNICATION ent, however, may a reply be tim Il expire SIX (6) MONTHS from ication to become ABANDONEI	I. lely filed the mailing date of this c (35 U.S.C. § 133).		
Status						
2a)						
Disposition of Claims						
 4) Claim(s) 23-44,47,48,102-106 and 142 is/are pending in the application. 4a) Of the above claim(s) is/are withdrawn from consideration. 5) Claim(s) is/are allowed. 6) Claim(s) 23-28, 30-36, 38-41, 44, 47-48, 102-106 and 142 is/are rejected. 7) Claim(s) 29,37,42 and 43 is/are objected to. 8) Claim(s) are subject to restriction and/or election requirement. 						
Applicatio	n Papers					
10)□ TI A R	ne specification is objected to by the Exhe drawing(s) filed on is/are: a)[applicant may not request that any objection leplacement drawing sheet(s) including the he oath or declaration is objected to by	accepted or b) to the drawing(s) be correction is require	e held in abeyance. See ed if the drawing(s) is obj	e 37 CFR 1.85(a). jected to. See 37 C		
Priority un	der 35 U.S.C. § 119					
 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f). a) All b) Some * c) None of: 1. Certified copies of the priority documents have been received. 2. Certified copies of the priority documents have been received in Application No 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)). * See the attached detailed Office action for a list of the certified copies not received. 						
2) Notice 3) Informa	of References Cited (PTO-892) of Draftsperson's Patent Drawing Review (PTO-9 of Draftsperson's Patement(s) (PTO-1449 or PTO-1449) No(s)/Mail Date 7/12/02: 11/17/03:47/04;	/SB/08)	4) Interview Summary Paper No(s)/Mail Da 5) Notice of Informal P 6) Other:	ate	O-152)	

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DETAILED ACTION

1. Prosecution on the merits of this application is reopened on claims 23-44, 47-48, 102-106 and 142 are considered unpatentable for the reasons indicated below.

- 2. Claims 23-44, 47-48, 102-106 and 142 are pending and under examination.
- 3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
- 4. This Office Action contains New Grounds of Rejections.

Specification

- 5. The substitute specification filed 10/28/2003 is acknowledged by the Examiner and has been entered.
- 6. The disclosure is objected to because of the following informalities:
- a. The disclosure is objected to because it contains embedded hyperlinks and/or other form of browser-executable code. For example, see page 36, line 12 (of specification filed 10/28/03). Applicant's cooperation is requested in reviewing the entire disclosure and delete all the embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01. Applicant is advised that the amendment to the specification should be directed to the page and line number of the specification filed 10/28/2003.
- b. The specification filed 10/28/03 at page 40, line 3 discloses USSN 07/723,454, which should be updated as "now abandoned". Applicant' cooperation is requested in

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reviewing the entire disclosure for additional US Application numbers that require correction.

c. Figure 7 contains parts A-D, however, the Brief Description of the Drawings only describes parts A and B. Again, any amendment should be directed to the Brief Description of the Drawings filed 10/28/03.

Appropriate correction is required.

New Grounds of Objection/Rejections

7. The substitute specification filed on 28 October 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The amendment claims priority to US Provisional Application No. 60/367,358 (formerly USSN 09/765,208, filed January 17, 2001). The priority application cannot be incorporated by reference after the original filing of the instant application. This objection can be overcome by removing the incorporation by reference statement.

See United States Patent and Trademark Office OG Notices: 1268 OG 89 (18 March 2003) "Benefit of Prior-Filed Application" (see Part VII).

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 44 and 47 are objected to as being dependent upon a cancelled claim.
 Appropriate correction is required.

9. Claim 44 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 44 recites the limitation "The protein". There is insufficient antecedent basis for this limitation in the claim. Assuming that the claim depends from a pending claim, all of the pending claims recite a single chain protein. Amending the limitation "The protein" to recite "The single chain protein" as well as correcting the claim dependency would overcome this rejection.

Priority

Applicant's benefit claim for priority of US Provisional Application No. 60/367,358 (formerly USSN 09/765,208, filed January 17, 2001) is acknowledged, however, US Provisional Application No. 60/367,358 does not contain adequate written support of the presently claimed single chain proteins. US Provisional Application No. 60/367,358 discloses the anti-CD20 2H7 scFv fused to human IgG1 hinge-CH2-CH3 as well as 2H7 scFv fused with CD154. Thus, priority application US Provisional Application No. 60/367,358 does not support the broader claims of the present application. Therefore, the effective filing date of the presently claimed subject matter is deemed to be that of the instant application, i.e., 1/17/2002. If applicant desires priority prior to 1/17/2002; applicant is invited to point out and provide documentary support for the priority of the instant claims. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

- (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
- 11. Claims 23-26 and 31-33 are rejected under 35 U.S.C. 102(e) as being anticipated by Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04).

The claims are summarized as a single chain protein comprising a binding domain polypeptide capable of binding a target, wherein the binding polypeptide is joined to a hinge peptide that is joined to an immunoglobulin CH2 constant region polypeptide that is joined to an immunoglobulin heavy chain CH3 constant region polypeptide, wherein said hinge region is an IgG or IgA hinge peptide that contains one or two cysteine residues, provided that when the hinge peptide contains two cysteines the first cysteine of the hinge that is responsible for forming a disulfide bond with a light chain constant region in a naturally-occurring IgG or IgA antibody is not deleted or substituted with an amino acid, wherein the single chain protein is capable of binding to said target and is capable of promoting ADCC or complement fixation or both. Further, the claims recite wherein the single chain protein is capable of depleting a population of target cells and capable of decreasing the number of target cells in vivo and in vitro.

Gillies et al teach single-chain antibodies (i.e., binding domain polypeptide capable of binding a target) fused to a hinge region fused to CH2 and CH3 domains,

wherein the hinge can be modified to have only one cysteine (i.e., first or N-terminal cysteine is mutated to a serine; see paragraphs [0100-0101]) or is from IgG1 (i.e., two cysteines; see Gilles paragraphs [0101] and [0112]) or IgA (see paragraph [0112]) (see paragraphs [0013, 0015, 0078, 0081, 0099-0101, 0112 and 0115]; all adequately supported in the Gillies provisional application). Gillies discloses a hybrid immunoglobulin includes an IgG1 hinge and IgG2 CH2 and CH3 domains and the IgG1 hinge region is advantageous since it only contains two hinge cysteines (see paragraphs [0081] and [0115]). The recitation that the single chain protein is (1) "capable of" binding a target and (2) "capable of" promoting ADCC or complement fixation or both are intended use limitations that do not distinguish over the prior art because the single-chain antibodies of Gillies are "capable of" binding a target and the heavy chain constant regions are responsible for Fc receptor binding and complement fixation (Gilles, end of paragraph [0085]). Thus, the single-chain antibodies of Gillies are also "capable of" depleting a population of cells and "capable of" decreasing the number of target cells in vivo and in vitro. "(T)he recitation of a new intended use for an old product does not make a claim to that old product patentable." In re Schreiber, 44 USPQ2d 1429 (Fed. Cir. 1997).

Thus, Gillies et al anticipate the claims.

12. Claims 39 and 142 are rejected under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of Immunology 162(11):6589-6595, 1999, IDS reference EA filed 7/12/02).

Claims 39 and 142 are drawn to said single chain protein wherein the binding domain polypeptide is a single-chain Fv (scFv) capable of binding CD20 wherein the hinge contains one or two cysteines that have been deleted or substituted with non-cysteine amino acid residues and wherein the heavy chain CH2 and CH3 domain are IgG1 CH2 and CH3 domains and one or both of said CH2 and CH3 domains are from human IgG1.

Shan et al teach a scFv-lg protein that binds CD20 on B cells, wherein the scFv comprises the VH and VL domains of monoclonal antibody 1F5 joined by a linker of 15 amino acids (i.e., binding domain polypeptide), and the scFv is fused to the hinge-CH2-CH3 of human IgG1, wherein the hinge cysteines are mutated to serines (see entire document, particularly Fig. 3, and page 6590, left column). Thus, the 1F5 scFv-lg of Shan is a single-chain protein comprising a binding domain polypeptide joined to a hinge peptide, which is joined to immunoglobulin CH2 and CH3 domains, wherein the hinge is an IgG hinge peptide containing two cysteines that have been substituted with non-cysteine amino acid residues and both CH2 and CH3 domains are human IgG1 and the single chain binds CD20 (i.e., capable of binding CD20) and is capable of promoting ADCC or complement fixation or both (see Fig 9 and page 6594, right column).

Thus, Stan et al anticipate the claims.

13. Claims 23-28, 31-34, 39 and 142 are rejected under 35 U.S.C. 102(a) as being anticipated by Wu et al (Protein Engineering 14(12):1025-1033, 2001, IDS filed 6/7/04).

The claims have been described supra.

Claims 27-28 and 34 recite wherein the single chain protein is capable of binding the B cell target, CD20 and the heavy and light chain variable regions of the single chain Fv are joined by a linker of at least about 6 amino acids.

Wu et al teach an anti-CD20 single-chain Fv-Fc fusion protein comprising the hinge-CH2-CH3 of human IgG1, wherein the upper hinge cysteine (Cys233; normally forms disulfide with the light chain) is mutated to serine and the variable regions of the single-chain Fv are joined by a linker of at 8 or 18 amino acids (i.e., at least about 6 amino acids) (see entire document, particularly Fig. 1, pg. 1026, bridging paragraph of left and right columns). Wu et al teach that the anti-CD20 single-chain Fv-Fc fusion protein binds CD20 and showed high complement-dependent cytolytic activity and thus, is "capable of" binding a B cell target and is "capable of" promoting complement fixation (see page 1032, bottom of left column).

Thus, Wu et al anticipate the claims.

14. Claims 27-28, 34, 40-41, 44, 47 and 102-103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Shan et al (The Journal of immunology, 162:6589-6595, 1999, IDS reference EA filed 7/12/02) and Liu et al (The Journal of Immunology, 139(10):3521-3526, 1987, IDS filed 6/7/04).

The claims are summarized as the single chain protein binds CD20 for treatment of B-cell disorder and has a linker of at least 6 amino acids, and wherein the hinge contains one or more serine residues in place of one or more cysteine residues.

Gillies et al has been described supra. Gillies et al does not teach a single chain binding to the B cell target, CD20, or a linker of at least 6 amino acids or the 2H7 scFv. These deficiencies are made up for in the teachings in Shan et al and Liu et al.

Shan et al has been described supra.

Liu et al teach the VH and Vk sequences of monoclonal antibody 2H7 that specifically targets CD20 expressed on B cell lymphomas.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a single chain protein comprising a CD20 specific scFv binding domain fused to a human IgG1 or IgA hinge joined to human IgG1 CH2 and CH3 domains, wherein the CD20 specific scFv comprises the 2H7 VH and Vk sequences for immunotherapy of B cell lymphomas in view of Gillies et al, Shan et al, and Liu et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a single chain protein comprising a CD20 specific scFv binding domain fused to a human IgG1 or IgA hinge joined to human IgG1 CH2 and CH3 domains, wherein the CD20 specific scFv comprises the 2H7 VH and Vk sequences for immunotherapy of B cell lymphomas in view of Gillies et al and Shan et al and Liu et al because Gillies et al teach single chain antibodies linked to an IgG1 or IgA hinge wherein one or more

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cysteines are mutated to non-cysteine amino acid residues (preferably serine) and Shan et al teach an anti-CD20 scFv-lgG1 wherein the VH and VL domains are joined by a 15 amino acid linker and Liu et al teach the VH and Vk sequences of monoclonal antibody 2H7 that specifically targets CD20 expressed on B cell lymphomas. Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to have mutated one or more hinge region cysteines because a high number of cysteines can lead to incorrect assembly of the Ig fusion protein according to Gilles et al. (see pg. 7, paragraph [0100]) and to target the B cell lymphoma antigen, CD20, for immunotherapy because CD20 antibodies do not internalize after cell surface binding. anti-CD20 antibodies are not shed from the cell surface and CD20 is expressed at a high density on more than 95% of all B cell lymphomas and the antigenic density of CD20 is relatively homogenous from one tumor to another (see Shan et al, pg. 6594. top left column). Thus, it would have been prima facie obvious to one skilled in the art at the time the invention was made to produce to have produced a single chain protein comprising a CD20 specific scFv binding domain fused to a human IgG1 or IgA hinge joined to human IgG1 CH2 and CH3 domains, wherein the CD20 specific scFv comprises the 2H7 VH and Vk sequences for immunotherapy of B cell lymphomas in view of Gillies et al and Shan et al and Liu et al

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references.

15. Claims 30, 35-36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Kucherlapati et al (US Patent 6,150,584, filed 10/2/96) and Gilliand et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04).

The claims further limit base claims 23, 24 and 25 wherein the scFv binds CD30 ligand, IL-12, or is capable of binding CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 or CEA.

Gillies et al have been described supra. Gillies et al does not teach a scFv binds CD30 ligand, IL-12, or is capable of binding CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 or CEA. These deficiencies are made up for in the teachings in Kucherlapati et al and Gilliand et al.

Kucherlapati et al teach single-chain antibodies that bind a wide range of therapeutic antigens including CD30 ligand, IL-12, CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 or CEA (see columns 9-10 and column 7, lines 40-43).

Gilliand et al teach scFv-lg fusion proteins (i.e., scFv-lgG1 hinge-CH2-CH3 fusion) and scFv are smaller than native antibody and are therefore less immunogenic and hence is better suited for therapeutic applications than whole antibodies (see entire document, especially page 2, left column and page 14). Gilliand teach a method of

rapidly cloning VH and VL from any hybridoma (see page 15, left columns and page 2, right column).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a single chain protein comprising a binding domain fused to human IgG1 hinge-CH2-CH3 having one or two hinge cysteines as taught by Gillies et al that bound the antigens taught by Kucherlapati et al for human therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a single chain protein comprising a binding domain fused to human IgG1 hinge-CH2-CH3 having one or two hinge cysteines as taught by Gillies et al that bound the antigens taught by Kucherlapati et al for immunotherapy because Gillies et al teach single chain antibodies linked to an IgG1 hinge wherein one or more cysteines are mutated to non-cysteine amino acid residues (preferably serine) and Kucherlapati et al teach single-chain antibodies that bind a wide range of therapeutic antigens including CD30 ligand, IL-12, CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 or CEA and Gilliand et al. teach scFv-Ig fusion proteins and scFv are smaller than native antibody and are therefore less immunogenic and hence, better suited for therapeutic applications than whole antibodies. Therefore, one of ordinary skill in the art would have been motivated at the time the invention was made to target the therapeutic antigens of Kucherlapati et al as a scFv-lg fusion protein as taught by Gillies and Gilliand because scFv are smaller

than native antibody and are therefore less immunogenic and better suited for therapeutic applications than whole antibodies. Thus, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to have produced a single chain protein comprising a binding domain fused to human IgG1 hinge-CH2-CH3 having one or two hinge cysteines that bind a therapeutic antigens selected from CD30 ligand, IL-12, CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 and CEA for immunotherapy in view of Gillies et al and Kucherlapati et al and Gilliand et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references.

16. Claims 48 and 104-106 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (U. S. Patent Application Publication US 2003/0044423A1, with priority to 60/274,096, 3/7/01, cited on PTO-892 mailed 8/27/04) in view of Fell et al (The Journal of Biological Chemistry, 267(22):15552-15558, 1992) and Gilliand et al (Tissue Antigens, 47:1-20, 1996, IDS filed 6/7/04).

The claims further limit base claims 23, 24 and 25 wherein the scFv binds CD30 ligand, IL-12, or is capable of binding CD2, CD5, CD27, CD28, CD40, CTLA-4, IL-4, CD72, CD86/B7.2, CD40 ligand, VLA-4, HER2, EGFR, VEGF, VEGFR, MUC-1 or CEA.

Gillies et al have been described supra. Gillies et al do not teach a scFv capable of binding L6 carcinoma antigen. These deficiencies are made up for in the teachings in Fell et al and Gilliand et al.

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Fell et al teach the L6 heavy and light chain variable regions of the L6 monoclonal antibody that binds the L6 antigen present on carcinomas of the breast, colon, lung and ovary (see entire document, especially Fig. 4 and pages 15556-15557).

Gilliand et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH2-CH3 or comprising an IgA hinge, wherein the hinge has one or two cysteines as taught by Gillies et al for human tumor therapy.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH2-CH3 or comprising an IgA hinge, wherein the hinge has one or two cysteines for human tumor therapy in view of Gillies et al and Fell et al and Gilliand et al because Gillies et al teach single chain antibodies linked to an IgG1 or IgA hinge wherein one or more cysteines are mutated to non-cysteine amino acid residues (preferably serine) and Fell et al teach the L6 heavy and light chain variable regions of the L6 monoclonal antibody that binds the L6 antigen present on carcinomas of the breast, colon, lung and ovary and Gilliand et al teach scFv-Ig fusion proteins and scFv are smaller and hence, less immunogenic than native antibody, and exhibit increased tumor penetration and localization in comparison to intact antibody or Fab fragments. Therefore, one of ordinary skill in the art would have been motivated at the time the

invention was made to produce an L6 carcinoma antigen specific scFv-lg fusion protein comprising only one or two hinge cysteines to reduce incorrect disulfide bond formation during heavy chain homodimerization as taught by Gillies (see page 7, paragraph [0100]) and for increased tumor penetration and localization and decreased immunogenicity as taught by Gilliand (pg. 2, left column). Thus, it would have been prima facie obvious to one skilled in the art at the time the invention was made to have produced a single chain protein comprising an L6 carcinoma antigen specific scFv fused to human IgG1 hinge-CH2-CH3 or comprising an IgA hinge, wherein the hinge has one or two cysteines for human tumor therapy in view of Gillies et al and Fell et al and Gilliand et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced from the references.

Conclusion

- 17. Claims 29, 37 and 42-43 are objected to as being dependent upon a rejected claim.
- 18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at

(571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully, David J. Blanchard 571-272-0827

thank Blook

LARRY R. HELMS, PH.D. SUPERVISORY PATENT EXAMINER Page 16